and 15 remain presented for examination. Support for the amended claims may be found throughout the specification and in the original claims. Reconsideration and withdrawal of the present rejections in view of the amendments and arguments presented herein is respectfully requested.

Discussion of Rejections Under §§ 112 and 101

The rejections under §§ 112 and 101 fail under the new GUIDELINES FOR EXAMINATION OF APPLICATIONS FOR COMPLIANCE WITH THE UTILITY REQUIREMENT. The Guidelines are relevant to whether an invention is patentable under § 112 as well as § 101. For example, the Examiner combines her rejection under § 112 with the rejection under § 101. Office Action at page 9. The relevance of the Guidelines to both statutory requirements is underscored by patent law.

The "how to use" requirement of § 112, ¶ 1, implicates whether an invention is operable, or useful, as broadly as it is claimed. The question of operability can be raised under both § 112 and § 101. In re Fouche, 169 U.S.P.Q. 429, 434 (C.C.P.A. 1971). It is considered to be the same rejection, whether made under § 112 or § 101. Ex parte Aggarwal, 23 U.S.P.Q.2d 1334, 1337 (Bd. Pat. App. Int. 1992). In this regard, then, the Guidelines are relevant to whether the claimed invention is considered to be operable, or useful, under both §§ 112 and 101.

According to these Guidelines, the P.T.O. is obligated to accept a statement of utility unless it is "incredible" in view of

contemporary knowledge. The present specification asserts that the disclosed method is useful in treatments involving inhibition of restenosis, and demonstrates that usefulness in a pig model. This statement must be accepted by the P.T.O., because those with ordinary skill in the art accept the disclosed pig model as the most correlatable predictor of human efficacy in treatments involving inhibition of restenosis.

Presented herewith is the Declaration of Dr. Elizabeth Nabel, M.D., who has been engaged in cardiovascular research for the past 10 years, has authored approximately 60 publications in peer-reviewed scientific journals, and is currently Professor of Internal Medicine and Director of the Cardiovascular Research Center at University of Michigan. Dr. Nabel reports that "the pig model is the most correlatable predictor of human efficacy in treatments involving inhibition of restenosis." Nabel Decl. ¶ 8.

Additionally, Applicants submit Schwartz et al., *Circulation*, **82**:2190-2200, 1990 (Exhibit A), Ferrell et al., *Circulation*, 85:1630-1631, 1992 (Exhibit B), and Schneider et al., *Circulation*, 88:628-637, 1993 (Exhibit C), which corroborate Dr. Nabel's statement that the pig model is the most correlatable predictor of human efficacy in treatments involving inhibition of restenosis. For example, Schwartz et al., at page 2190, column 1, indicates that "an experimental animal model of human coronary restenosis developed in domestic swine [] accurately mimics the proliferative component of human restenosis . . . ." Additionally, Ferrell et

al., at page 1630, column 2, states that "most of the data obtained in the pig . . . model[] of restenosis after PTCA, contrary to those obtained in the smaller size of the animal species, appear to be more closely related to the data obtained in humans." Moreover, Ferrell et al., at page 1631, column 1, reports that "research conducted in the pig . . . appears to be the most predictive of results in humans . . . ." Finally, Schneider et al. describe the specific advantages of the swine model over other animal models for the study of restenosis, including similarities with the human coronary circulation, the spontaneous development of atherosclerosis, and the response to vascular injury (p. 629, column 1).

Under the new Guidelines, credibility is to be assessed from the perspective of one of ordinary skill in the art. Given that perspective, which is elaborated above, Applicants' assertion that the disclosed method is useful in inhibiting restenosis, the utility of which has been demonstrated in an art-accepted animal model, must be accepted as credible. Accordingly, the §§ 112 and 101 rejections should be reconsidered and withdrawn.

For the sake of completeness, Applicants address the Examiner's other points.

The P.T.O. alleged that it was unlikely that others would correlate the animal data presented in the specification with a therapeutic effect in view of the "small sample size and individual species differences." It is common practice to investigate a

do the exhibits reflect disclosed + claimed protocols

smaller number of pigs compared to other smaller experimental animals. Nabel Decl. ¶ 9. The studies described in the specification have now been performed in 30 pigs, 60 rabbits and 31 rats. The pig study is described by Ohno et al., *Science*, 265:781-784, 1994 (Exhibit D). The rabbit study is summarized in the enclosed unpublished data from Dr. Nabel's laboratory (Exhibit E). The rat study is described in the accompanying manuscript in press in *Mol. Med.* (Exhibit F). No significant species differences were observed in either intimal area or reduction in cellular proliferation. Nabel Decl. ¶ 9. Similar numbers of animals have been used by other investigators. Id. Thus, the animal data is correlatable.

The Examiner maintained that the animal data is not predictive, because "long-term studies have not been carried out." Ohno et al., supra, however, present long-term studies demonstrating that "reduction in intimal hyperplasia was stable." Ohno et al., at page 782. Therefore, the animal data is predictive.

The P.T.O. contended that the "specification fails to enable human gene therapy." Applicants do not claim human gene therapy per se. Consequently, the contention is irrelevant.

The Examiner asserted, in reference to Morishita et al., that no effective pharmacological therapy for preventing restenosis in humans had been reported and that this failure may reflect previous difficulty in identifying appropriate drug targets. Distinct

differences exist, however between Applicants' adenovirus approach and the antisense approach of Morishita et al. Nabel Decl. ¶ 10. In an antisense approach, the oligonucleotide must be delivered intracellularly to a sufficient number of cells to inhibit restenosis, since the oligonucleotide has its effects within a single cell and not in adjacent cells. Id. In contrast, Applicants' approach is effective in both transfected cells and in adjacent dividing cells by a bystander effect as defined below. Id. The elimination of dividing cells can be achieved by expressing the tk gene in dividing vascular smooth muscle cells (SMCs). Id. tk converts GCV into an active toxic form in SMCs. Id. The subsequent incorporation of phosphorylated GCV into DNA results in cell death by inducing chain termination. Id. In SMCs, a metabolite of phosphorylated GCV is diffusible to adjacent dividing SMCs, resulting in cell death in dividing SMCs not expressing tk. Id. The end result is called a "bystander effect" which refers to the amplified response within a larger number of dividing SMCs. Id. Thus, expression of tk in dividing SMCs following adenoviral infection and treatment with GCV kills adjacent dividing nontransduced SMCs through a bystander effect, thus amplifying the response and permitting the killing of a larger number of SMCs. Id. Accordingly, the antisense approach of Morishita et al. is irrelevant to Applicants' adenovirus approach.

The P.T.O. stated that the specification failed to adequately describe the cytosine deaminase gene and how to make and use

vectors incorporating the gene. Applicants do not agree with the grounds of rejection. To expedite prosecution of the application and advance the case towards allowance, however, Claims 16 and 17 directed to the cytosine deaminase gene have been canceled.

The Examiner queried whether deposit of the Ad.HSV-tk vector was necessary for enablement. This vector is obtainable by a repeatable method set forth in the specification. Hence, under Amgen Inc. v. Chugai Pharmaceutical Co., 18 U.S.P.Q.2d 1016, 1024-25 (Fed. Cir.), cert. denied, 112 S. Ct. 169 (1991), deposit is not necessary for enablement.

The P.T.O. stated that the specification did not adequately disclose how to make and use adenoviral vectors in general, non-adenoviral vectors, vector-liposome or vector-ligand conjugates. The construction and use of these vectors, however, is well known in the art. Nabel Decl. ¶ 11. For example, the construction of other adenoviral vectors requires only a different cDNA insert. Id. The adenovirus, restriction sites and ligation techniques are the same regardless of the cDNA to be expressed. Id. Nonadenoviral vectors, vector-liposome and vector-ligand conjugates are also well known in the art.

The statement by Lee et al. that "the level of gene transfer resulting from lipofection of the plasmid was far below that obtained with the Av1LacA4 vector" does not reflect the current state of the art. Lee et al. compared the efficiency of gene transfer of an adenoviral vector encoding a reporter gene and a

plasmid encoding a reporter gene mixed with Lipofectin, a first generation cationic liposome. Nabel Decl. ¶ 12. This liposome preparation is not as effective as current second and third generation cationic liposomes. Id. Thus, the low level of gene transfer obtained by Lee et al. using lipofection could not be considered an obstacle by those skilled in the art in view of the improved liposome reagents currently available. Id.

The P.T.O. postulated that the delivery of a vector at the time of angioplasty or other mechanical damage may be insufficient to transduce a sufficient quantity of cells to achieve the result of the exemplified adenoviral vector. It pointed to the Takeshita et al. abstract, which indicates that active cell proliferation augments the efficiency of gene transfer and that DNA:Lipofectin-mediated transfection was far more efficient if administered at 3-14 days post-arterial denudation. The claims, however, do not recite that the method must be the most efficient.

Moreover, Applicants agree that active cell proliferation augments gene transfer. The specification, at page 11, lines 29-33, discloses that cell proliferation in the arterial intima was first evident approximately 24-48 hours after balloon injury, peaked at 4 days and continued actively through day 7. Thus, active cell proliferation is occurring at the time of recombinant gene transfer and expression. The P.T.O.'s postulate that delivery of the vector at the time of angioplasty may be insufficient to achieve an efficacious result is erroneous, as the data in the

instant specification demonstrate that delivery of the vector at the time of angioplasty is indeed sufficient to transduce a sufficient quantity of cells to achieve inhibition of restenosis.

In any event, the claims do not contain a requirement for simultaneity. Following Applicants' success, those with ordinary skill in the art may adjust Example 7 to wait several days post-arterial denudation before transfection. On balance, the benefit of catheterization followed by immediate transfection may outweigh the risk of catheterization followed by post-operative transfection, and the physician, together with the patient, should make this call. Both embodiments, however, are contemplated by the specification as evidenced by the express claim language.

Only 4 guidance is present

Finally, the P.T.O. alleged that the specification was not enabling for any and all "mechanical means" of injury. The claimed method applies to all mechanical means of injury, since all would result in subsequent vascular smooth muscle cell proliferation and intimal thickening. Nabel Decl. ¶ 13. These are generic responses which occur after single or double injuries, whether by laser, balloon or stent. Id.

The Santoian et al. publication cited by the P.T.O. does not support its allegation. Rather, Santoian et al. corroborates the Nabel Declaration. Santoian et al. reports that intimal hyperplasia is the hallmark of restenosis, as it is produced by three different mechanical injury models, including balloon injury, balloon injury followed by repeat balloon injury, and balloon

injury followed by stent placement. Thus, Santoian et al. actually supports enablement of the invention for any and all "mechanical means" of injury.

In view of the arguments presented above, Applicants respectfully request reconsideration and withdrawal of the rejections under §§ 112 and 101.

Discussion of Rejections Under § 112, second paragraph

The P.T.O. rejected Claims 1 and 16, stating that the phrase "preferentially incorporating" was indefinite. Claim 1 has been amended to recite "wherein said analog is preferentially incorporated into the DNA . . .", clearly indicating that this step is performed by the analog. Claim 4 has been amended as suggested by the Examiner. Claim 7 has been amended to recite single elements and to delete reference to "other necessary adenoviral genes". Claim 12 has been amended to refer to the "nucleoside analog" rather than the "suicide compound", thus providing proper antecedent basis. Claim 14 has been amended to correct its dependency and to provide proper antecedent basis by referring to the analog rather than the compound.

In view of the above-indicated claim amendments, Applicants submit that all claims are fully definite and respectfully request withdrawal of all rejections under § 112, second paragraph.

Discussion of Rejection Under § 102(b)

The Examiner rejected Claims 18-19 as being anticipated by Haj-Ahmad et al. Applicants do not agree with the grounds of

rejection. To expedite prosecution of the application and advance the case towards allowance, however, these claims have been canceled.

Discussion of Rejections Under § 103

The P.T.O. rejected Claims 1, 2, and 12-15, taking the initial position that they were unpatentable over Takeshita et al. (abstract 3179) in view of Plautz et al. According to the P.T.O., Takeshita et al. discloses the claimed invention with the exception of the tk gene, and, further according to the P.T.O., it would have been obvious to substitute the tk gene of Plautz et al.

Takeshita et al. is, however, directed to the effect of angioplasty on transfection efficiency of the marker gene luciferase, not to restenosis. The treated lesions showed a reduction in stenosis, not "a reduction of restenosis," as contended by the P.T.O. Nabel Decl. ¶ 14. The reduction in stenosis diameter following balloon injury is due to the injury itself, and is a common response to balloon angioplasty. Id. Restenosis is defined as the recurrence of a stenosis, and was not evaluated by Takeshita et al. Id. The P.T.O.'s allegation, that this abstract discloses the claimed invention with the exception of the tk gene, is simply incorrect.

Moreover, Plautz et al. is non-analogous art, because it is not within the field of the present inventors' endeavor, and it is not reasonably pertinent to the particular problem with which the inventors were involved. In re Clay, 23 U.S.P.Q.2d 1058, 1061

(Fed. Cir. 1992). Plautz et al. describes the use of the tk gene for treatment of proliferating tumor cells. This field of endeavor is therefore the field of cancer research. In contrast, Applicants' field of endeavor is the field of cardiovascular research. Cancer research cannot be considered to be the same field of endeavor as cardiovascular research.

Neither are their purposes alike to recommend Plautz et al. to Applicants. The treatment of Plautz et al. addresses problems unique to cancer cells. Such problems are not reasonably pertinent to the problems with which Applicants were involved - those unique to cells of the cardiovasculature. Since Plautz et al. is non-analogous art, the rejection cannot be sustained in view of this publication either.

The P.T.O. rejected Claims 16 and 17, stating that they were unpatentable over Takeshita et al. in view of Plautz et al. and further in view of Mullen et al. These claims were canceled, as elaborated above.

Claims 3-5 and 8 were rejected by the P.T.O., which contended that they were unpatentable over Takeshita et al. in view of Plautz et al. and further in view of Willard et al. Claims 9 and 11 were rejected as being unpatentable over Takeshita et al. in view of Plautz et al. and further in view of Willard et al. and Curiel et al. Claims 6 and 20 were rejected as being unpatentable over Takeshita et al. in view of Plautz et al. further in view of Willard et al. and Herbomel et al.

As detailed above, Takeshita et al. and Plautz et al. do not support an obviousness rejection. Thus, any combination of references relying on these two references fails, also, to render the claimed invention unpatentable.

In view of the arguments presented above, Applicants respectfully request reconsideration and withdrawal of all rejections under § 103.

Conclusion

Applicants have made a good faith effort to respond to all issues raised in the Office Action. However, if minor matters remain, the Examiner is invited to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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